

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
16 June 2005 (16.06.2005)

PCT

(10) International Publication Number
WO 2005/054236 A1

(51) International Patent Classification⁷: **C07D 471/04**,
519/00, C07K 5/00, C07H 21/00, A61P 35/00, A61K
31/4745

(74) Common Representative: **CRYSTAX PHARMACEU-
TICALS S.L.**; JUNGHANS, Claas, Josep Samitier 1-5,
E-08028 Barcelona (ES).

(21) International Application Number:
PCT/EP2004/013106

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

(22) International Filing Date:
18 November 2004 (18.11.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P200302821 20 November 2003 (20.11.2003) ES

(71) Applicants (for all designated States except US): **CRYSTAX PHARMACEUTICALS S.L.** [ES/ES]; Josep Samitier 1-5, E-08028 Barcelona (ES). **CONSEJO SUPERIOR DE INVESTIGACIONES CIENTIFICAS** [ES/ES]; Serrano, 113, 28006 Madrid (ES). **UNIVERSITAT POLITÈCNICA DE CATALUNYA** [ES/ES]; Jordi Girona, 31, E-8034 Barcelona (ES).

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LU, MC, NL, PL, PT, RO, SE,
SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **AYMAMI BO-FARULL, Juan** [ES/ES]; Universitat Politècnica de Catalunya, Jordi Girona, 31, E-08034 Barcelona (ES). **COLL CAPELLA, Miquel** [ES/ES]; Consejo Superior de Investigaciones Científicas, Serrano, 113, E-28006 Madrid (ES). **LLEBARIA SOLDEVILA, Amadeo** [ES/ES]; Consejo Superior de Investigaciones Científicas, Serrano, 113, E-28006 Madrid (ES). **NAVARRO MUÑOZ, Isabel** [ES/ES]; Crystax Pharmaceuticals, S.L., Parc Científic de Barcelona, Josep Samitier 1-5, E-08028 Barcelona (ES).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designation US
- of inventorship (Rule 4.17(iv)) for US only

Published:

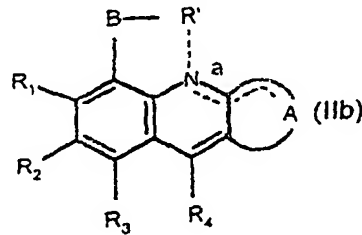
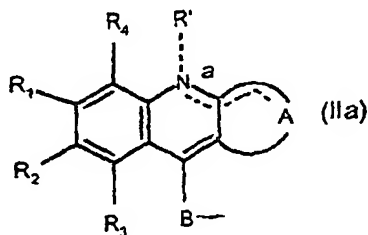
- with international search report
- with amended claims and statement

Date of publication of the amended claims and statement:

18 August 2005

[Continued on next page]

(54) Title: SUBSTITUTED QUINOLINES FOR THE TREATMENT OF CANCER



(57) Abstract: Compounds of formula G_1-L-G_2 , where $-G_1$ is a radical structurally close to cryptolepine, $-L-$ is a single covalent bond or a covalent linking biradical selected from $(CH_2)_xNR''(CH_2)_y$ and $-(CH_2)_xNR'''(CH_2)_yNR'''(CH_2)_z-$, $-R''$ and $-R'''$ are radicals, same or different, selected from the group consisting of H and (C_1-C_3) -alkyl; x , y and z are an integer from 1 to 3 and, $-G_2$ is H or a radical structurally close to $-G_1$, are intercalators. They are compounds which intercalate between DNA base pairs, and are useful as therapeutic agents against cancer, as assessed by an *in vitro* test of cytotoxicity with human leukemia cells Jurkat E6-1 and human carcinoma cells GLC-4. Preferred compounds are those where $-G_1$ is bonded to $-L-$ through a carbonyl amino and $-L-$ is $-(CH_2)_3NCH_3(CH_2)_3$ or $-(CH_2)_2NCH_3(CH_2)_3NCH_3(CH_2)_2-$ where $x = 2$ or 3. $-G_1$ is a radical selected from (IIa) and (IIb); $-G_2$ is a radical selected from H, a radical of formula (IIa), a radical of formula (IIb), the N-radical of 1,8-naphthalimide, the C4-radical of 2-phenylquinoline, and the C9-radical of acridine.

WO 2005/054236 A1



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.